22. 2-*Bromomethylnicotinates: Reaction with Nucleophilic Reagents.*

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Treatment of ethyl 2-methylnicotinate and ethyl 2-methyl-6-phenylnicotinate with *N*-bromosuccinimide has yielded the corresponding monobromomethylnicotinates. These compounds react readily with a series of nucleophilic reagents; where the initial products contained a group capable of intramolecular reaction with the ethoxycarbonyl substituent bicyclic compounds were obtained.

FOUR principal methods have been used for the preparation of monohalogenomethylpyridines. Direct halogenation is difficult to stop at the monosubstituted stage,[1] but Hammick [2] has shown that trihalogenomethylpyridines, the normal products of direct halogenation, can be reduced to the corresponding di- and mono-halogenomethylpyridines with tin and hydrochloric acid. The commonest method of preparing monohalogenomethylpyridines is by the action of a hydrohalogen acid [3] or a phosphorus halide [4] on

[1] Elderfield, " Heterocyclic Compounds," Wiley, 1950, Vol. I, p. 509.
[2] Hammick, *J.*, 1923, **123**, 2882.
[3] Bixler and Niemann, *J. Org. Chem.*, 1958, **23**, 581.
[4] Itai and Ogura, *J. Pharm. Soc. Japan*, 1955, **75**, 296.

hydroxymethylpyridines. 2-Chloromethylpyridine has been so obtained,[4] and also by the action of toluene-*p*-sulphonyl chloride on 2-picoline 1-oxide.[5] Hasegawa [6] has shown that 2-bromomethylpyridine may be prepared in 42% yield and isolated as its picrate by the action of *N*-bromosuccinimide on 2-picoline. Bromination of 2,6-dimethylpyridine by a similar method gave a 2% yield of 2,6-di(bromomethyl)pyridine together with some 2-bromomethyl-6-methylpyridine.[7]

We have shown that with ethyl 2-methylnicotinate and ethyl 2-methyl-6-phenylnicotinate monobromination with *N*-bromosuccinimide proceeds readily and in good yield. Ethyl 2-bromomethylnicotinate was a liquid which slowly darkened giving a red solid, such a change being probably due to intermolecular quaternisation.[8] Both of the bromomethylnicotinates have been shown to react with a typical series of nucleophilic reagents, the 6-phenylnicotinate requiring stronger reaction conditions. The reaction with sodium sulphite, in particular, was of interest in that the product, 3-ethoxycarbonyl-2-pyridylmethanesulphonic acid is the only recorded pyridylmethanesulphonic acid; its properties and those of the cyanomethylpyridines are being investigated further.

Where the initial product contained a group capable of cyclisation with the ethoxycarbonyl group bicyclic compounds were formed. Thus with sodium hydroxide or sulphuric acid, ethyl 2-bromomethylnicotinate yielded 2-hydroxymethylnicotinic lactone.[9,10] Sato *et al.* also prepared 2-anilinomethylnicotinic lactam by the action of aniline on 2-hydroxymethylnicotinic lactone but failed similarly to obtain 2-aminomethylnicotinic lactam. We have obtained these lactams by the action of aniline and ammonia, respectively, on ethyl 2-bromomethylnicotinate. Treatment of the hexamine adduct of ethyl 2-bromomethylnicotinate with ethanolic hydrogen chloride gave the same 2-aminomethylnicotinic lactam. Ethyl 2-bromomethyl-6-phenylnicotinate yielded similar bicyclic compounds. The expected initial product of the reaction of phenylhydrazine with ethyl 2-bromomethylnicotinate is ethyl 2-2′-phenylhydrazinomethyl nicotinate which could possibly cyclise to either a five- or a six-membered lactam. The product had a wide range of m. p.; repeated fractional crystallisation or chromotography on silica failed to narrow the m. p. range and it is presumed that both cyclic compounds were present.

Experimental

Ethyl 2-Bromomethylnicotinate.—Ethyl 2-methylnicotinate (10·0 g.), *N*-bromosuccinimide (15·0 g.), benzoyl peroxide (1·0 g.), and carbon tetrachloride (200 ml.) were refluxed for 6 hr. The suspension was filtered, and the filtrate washed successively with 4·0% sodium hydroxide, water, and 2·0% hydrochloric acid, and finally dried (Na_2SO_4). The solution was saturated with dry hydrogen chloride and the precipitated *ethyl 2-bromomethylnicotinate hydrochloride* (8·1 g.) collected. Crystallisation from ethanol gave prisms, m. p. 152—154° (decomp.) (Found: N, 5·0%; equiv., 280·5. $C_9H_{11}BrClNO_2$ requires N, 5·0%; equiv., 282). Ethyl 2-bromomethylnicotinate was isolated as a pale yellow oil by basification of an aqueous solution of the hydrochloride. It darkened on keeping and was therefore freshly prepared when required. The *picrate* crystallised from ethanol in yellow prisms, m. p. 125—127° (Found: C, 38·4; H, 3·1; N, 12·05. $C_{15}H_{13}BrN_4O_9$ requires C, 38·1; H, 2·8; N, 11·8%). Basification of the 2·0% hydrochloric acid extract yielded unchanged ethyl 2-methylnicotinate (0·3 g.), and evaporation of the carbon tetrachloride filtrate gave a red oil (3·7 g.) which was presumably crude ethyl 2-dibromomethylnicotinate.

Ethyl 2-Bromomethyl-6-phenylnicotinate.—Ethyl 2-methyl-6-phenylnicotinate (60·0 g.), *N*-bromosuccinimide (50·0 g.), benzoyl peroxide (2·0 g.), and carbon tetrachloride (250 ml.) were refluxed for 10 hr. The resulting suspension was filtered, and the filtrate washed with

[5] Matsumura, *J. Chem. Soc. Japan*, 1953, **74**, 363.
[6] Hasegawa, *Pharm. Bull. Japan*, 1953, **1**, 293.
[7] Barnes and Fales, *J. Amer. Chem. Soc.*, 1953, **75**, 3830.
[8] Sǒrm and Sedivý, *Coll. Czech. Chem. Comm.*, 1948, **13**, 288.
[9] Hemmerich and Fallah, *Helv. Chim. Acta*, 1958, **41**, 498.
[10] Sato, Iwashige, and Mujadera, *J. Pharm. Bull. Japan*, 1960, **8**, 427,

4·0% sodium hydroxide, then with water and finally concentrated. The residue was crystallised from ethanol to give the *bromomethyl* compound (44·0 g.) as cream prisms, m. p. 79—80° (Found: C, 56·1; H, 4·4; N, 4·4. $C_{15}H_{14}BrNO_2$ requires C, 56·3; H, 4·4; N, 4·4%), and unchanged ethyl 2-methyl-6-phenylnicotinate (4·1 g.), m. p. 43—44°.

2-*Hydroxymethylnicotinic Lactone.*—(*a*) Ethyl 2-bromomethylnicotinate hydrochloride (1·2 g.), potassium hydroxide (0·57 g.), and water (10·0 ml.) were stirred for 90 min. The resulting red solution was acidified to pH 3·0 and extracted with ether. Concentration of the ethereal extract gave the lactone (0·39 g.) crystallising from ethanol in needles, m. p. 141—142° (Found: C, 62·3; H, 3·5; N, 10·05. Calc. for $C_7H_5NO_2$: C, 62·2; H, 3·7; N, 10·4%). (*b*) Ethyl 2-bromomethylnicotinate (1·0 g.) and 30% sulphuric acid (5·0 ml.) were refluxed for 5 hr. The solution was adjusted to pH 3·0 and extracted with ether to give the lactone (0·31 g.), m. p. alone and on admixture with the product from (*a*), 141—142°. Sato *et al.*[10] give m. p. 141—142°.

2-*Hydroxymethyl-6-phenylnicotinic Lactone.*—Ethyl 2-bromomethyl-6-phenylnicotinate (1·0 g.) and 50% potassium hydroxide solution (10·0 ml.) were refluxed for 4 hr. The solid which had slowly separated dissolved on dilution with water (100 ml.). The diluted solution was acidified with hydrochloric acid to give the *lactone monohydrate* (0·6 g.), crystallising from aqueous ethanol in needles, m. p. 159—161° with loss of water of crystallisation (Found: C, 68·2; H, 5·0; N, 6·2. $C_{13}H_9NO_2,H_2O$ requires C, 68·1; H, 4·8; N, 6·1%). The lactone gave a positive hydroxamic acid test and a neutral solution in acetone.

2-*Aminomethylnicotinic Lactam.*—(*a*) A solution of ethyl 2-bromomethylnicotinate (1·8 g.) in chloroform (7·0 ml.) was treated with hexamine (1·1 g.) in chloroform (14·0 ml.). The mixture was stirred at room temperature for 1 hr. to give the *hexamine addition product* of ethyl 2-bromomethylnicotinate (2·0 g.), m. p. 142—144° (Found: C, 47·3; H, 5·9; N, 18·3. $C_{15}H_{22}BrN_5O_2$ requires C, 46·9; H, 5·7; N, 18·2%). The addition product (1·5 g.), ethanol (15·0 ml.), and hydrochloric acid (1·8 ml.) were refluxed for 1 hr. The precipitated ammonium chloride was filtered off, and the filtrate evaporated to dryness. The residue was stirred with potassium carbonate (1·0 g.) in the presence of chloroform, and the chloroform solution evaporated to give the lactam (0·8 g.) which separated from ethanol in needles, m. p. 204—206° (Found: C, 62·7; H, 4·6; N, 21·2. $C_7H_6N_2O$ requires C, 62·7; H, 4·5; N, 20·9%). (*b*) Ethyl 2-bromomethylnicotinate hydrochloride (1·0 g.) in ethanol (10·0 ml.) was treated with ammonia (*d* 0·88; 5·4 ml.), and the mixture stirred for 6 hr. The resulting solution was concentrated to low bulk and extracted with chloroform. The dried (Na_2SO_4) extract was evaporated to yield the lactam (0·31 g.), crystallising from ethanol in needles, m. p. 204—206° alone and on admixture with the product from (*a*).

2-*Aminomethyl-6-phenylnicotinic Lactam.*—(*a*) Similar reaction of ethyl 2-bromomethylnicotinate (1·6 g.) with hexamine gave the hexamine addition product (2·04 g.), m. p. 177—179°, which on treatment with alcohol and hydrochloric acid afforded the *lactam* (0·7 g.), prisms (from ethanol), m. p. 263—265° (Found: C, 74·5; H, 4·5; N, 13·4. $C_{13}H_{10}N_2O$ requires C, 74·2; H, 4·7; N, 13·3%). (*b*) Similar reaction of ethyl 2-bromomethyl-6-phenylnicotinate (3·2 g.) with ammonia and ethanol gave the lactam (1·3 g.), m. p. and mixed m. p. with the product from preparation (*a*) 263—265°.

Ethyl 2-*Cyanomethylnicotinate.*—Ethyl 2-bromomethylnicotinate (2·7 g.) in ethanol (7·0 ml.) was treated with potassium cyanide (1·35 g.) in water (6·0 ml.), and the solution stirred at room temperature for 2 hr. Water was added and the liberated oil extracted into ether. Evaporation of the extract gave the *nitrile* (2·0 g.) as a viscous oil hardening to a solid on prolonged cooling. Crystallisation from ethanol gave prisms, m. p. 67—68° (Found: C, 63·6; H, 5·6; N, 14·6. $C_{10}H_{10}N_2O_2$ requires C, 63·1; H, 5·3; N, 14·7%).

Ethyl 2-*Cyanomethyl-6-phenylnicotinate.*—Ethyl 2-bromomethyl-6-phenylnicotinate (8·0 g.) in ethanol (5·0 ml.) was treated with potassium cyanide (1·7 g.) in water (5·0 ml.), and the solution refluxed for 8 hr. Water (80·0 ml.) was added to precipitate a gum which was crystallised directly from ethanol to give the crude *nitrile* (5·6 g.; m. p. 83—87°). Recrystallisation from ethanol gave needles, m. p. 90—91° (Found: C, 72·2; H, 5·2; N, 10·4. $C_{16}H_{14}N_2O_2$ requires C, 72·2; H, 5·3; N, 10·5%).

3-*Ethoxycarbonyl-2-pyridylmethanesulphonic Acid.*—Ethyl 2-bromomethylnicotinate (1·0 g.) was added to a solution of sodium sulphite (0·86 g.) in water (6·0 ml.), and the mixture stirred at room temperature for 6 hr. The resulting solution was washed with ether, acidified, and concentrated to low volume to yield the *sulphonic acid* (0·62 g.), needles, m. p. 295—297°, from

water (charcoal) (Found: C, 44·2; H, 4·4; N, 5·3. $C_9H_{11}NO_5S$ requires C, 44·1; H, 4·5; N, 5·7%).

Ethyl 6-Phenyl-2-thiocyanatomethylnicotinate.—Ethyl 2-bromomethyl-6-phenylnicotinate (1·0 g.), potassium thiocyanate (0·5 g.), and ethanol (10·0 ml.) were refluxed for 30 min. The potassium bromide was removed by filtration and the filtrate cooled to give the *product* (0·56 g.), needles, m. p. 116—117°, from methanol (Found: C, 64·15; H, 4·7; N, 9·3. $C_{16}H_{14}N_2O_2S$ requires C, 64·4; H, 4·7; N, 9·4%).

Ethyl 2-(2,2-Diethoxycarbonylethyl)nicotinate.—Ethyl 2-bromomethylnicotinate (1·0 g.) was added to a solution of diethyl malonate (0·79 g.) and sodium ethoxide (from 0·1 g. of sodium) in ethanol (1·8 ml.), and the mixture stirred at room temperature for 1 hr. The ethanol was removed by distillation, the residue extracted with ether, and the extract evaporated. The resulting oil (1·0 g.) was distilled to give ethyl 2-(2,2-diethoxycarbonylethyl)nicotinate b. p. 156—157°/1·0 mm. The *picrate* had m. p. 72—73° (Found: C, 48·1; H, 5·0; N, 10·9. $C_{22}H_{24}N_4O_{13}$ requires C, 47·8; H, 4·4; N, 10·1%).

Ethyl 2-(2,2-Diethoxycarbonylethyl)-6-phenylnicotinate.—Ethyl 2-bromomethyl-6-phenylnicotinate (3·2 g.) was added to a solution of diethyl malonate (1·6 g.) and sodium ethoxide (from 0·23 g. of sodium) in ethanol (10·0 ml.). The mixture was refluxed for 5 hr. (neutral to damp litmus papers), and the ethanol distilled off and water added. The precipitate (3·1 g.) was collected and crystallised from ethanol to give *ethyl 2-(2,2-diethoxycarbonylethyl)-6-phenylnicotinate* as prisms, m. p. 122—123° (Found: C, 65·8; H, 6·1; N, 3·6. $C_{22}H_{25}NO_6$ requires C, 66·1; H, 6·3; N, 3·5%).

Ethyl 2-Naphthyloxymethylnicotinate.—Ethyl 2-bromomethylnicotinate (1·0 g.) was added to 2-naphthol (0·6 g.) in ethanol (2·0 ml.), the solution treated with sodium ethoxide (from 0·1 g. of sodium) in ethanol (1·8 ml.), and the mixture stirred at room temperature for 4 hr. Ether (20 ml.) was added, the precipitate filtered off, the filtrate washed with sodium hydroxide solution and then with water, dried (Na_2SO_4), and evaporated to give the naphthyl ether as a viscous oil. The *picrate* had m. p. 175—177° (Found: C, 55·7; H, 3·9; N, 10·5. $C_{25}H_{20}N_4O_{10}$ requires C, 55·9; H, 3·7; N, 10·5%).

Ethyl 2-Naphthyloxymethyl-6-phenylnicotinate.—Ethyl 2-bromomethyl-6-phenylnicotinate (0·8 g.), treated with 2-naphthol and sodium ethoxide under the above conditions, but refluxing the mixture for 7 hr. and working up as above gave the naphthyl ether as an oil (0·21 g.). The *picrate* had m. p. 141—142° (Found: C, 60·8; H, 4·4; N, 9·1. $C_{31}H_{24}N_4O_{10}$ requires C, 60·8; H, 3·9; N, 9·1%).

2-Anilinomethylnicotinic Lactam.—Ethyl 2-bromomethylnicotinate (1·0 g.), aniline (0·76 g.), and ethanol (5·0 ml.) were refluxed for 2 hr. Water was added and an oil (0·6 g.) separated which slowly solidified. Crystallisation from glacial acetic acid then alcohol yielded the lactam in needles, m. p. 179—181° (Found: C, 74·5; H, 4·8; N, 13·2. Calc. for $C_{13}H_{10}N_2O$: C, 74·3; H, 4·8; N, 13·3%). Sato *et al.*[10] give m. p. 180·5—181·5°.

2-Anilinomethyl-6-phenylnicotinic Lactam.—Ethyl 2-bromomethyl-6-phenylnicotinate (0·8 g.), aniline (0·48 g.), and ethanol (5·0 ml.) were refluxed for 6 hr. Cooling the solution yielded the *lactam* (0·48 g.) which crystallised from acetic acid in needles, m. p. 228—229° (Found: C, 79·3; H, 5·6; N, 9·6. $C_{19}H_{14}N_2O$ requires C, 79·7; H, 4·9; N, 9·8%).

Action of Phenylhydrazine on Ethyl 2-Bromomethylnicotinate.—Ethyl 2-bromomethylnicotinate (1·0 g.), phenylhydrazine (0·9 g.), and ethanol (5·0 ml.) were refluxed for 2 hr., cooled to room temperature, and the product (0·53 g.), m. p. 196—202°, collected. One crystallisation from ethanol raised the m. p. to 214—219° but further crystallisation from ethanol or acetic acid, or chromatography in benzene did not narrow the range of m. p. (Found: C, 69·0; H, 5·1; N, 18·9. Calc. for $C_{13}H_{11}N_3O$: C, 69·3; H, 4·9; N, 18·7%).

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